## REMARKS

Claims 22-45 are pending in this application. Claims 1-21 have been canceled without prejudice or disclaimer, and claims 22-45 have been added. Applicants reserve the right to pursue the canceled subject matter in later, to be filed applications.

Claims 22-45 have been added to more clearly define Applicants' invention. Support for the new claims can be found, at least for example, on page 2, paragraph 45; in Table 1 on page 49; in Table 2 on pages 126 and 130-31, 133-137, and 144; page 218, paragraph 283; and pages 587-89; and in original claim 1, sections (n) and (o). Therefore, claims 22-45 are fully supported by the application as filed.

Applicants respond to each issue raised in the Office Action dated November 26, 2004.

### Restriction Requirement

Applicants confirm, with traverse, the oral election of Group I, claims 1-18, drawn to fusion proteins and methods of use. Applicants have replaced the previously pending claims 1-18 with new claims 22-45, that all fall within the Group I, and better define the present invention.

### Requests to Change Inventorship

Applicants have filed concurrently herewith two requests to change the inventorship of the instant application.

First, Applicants have filed a Request to Add Inventor Under 37 C.F.R. § 1.48(a) to add Steven M. Ruben to the originally filed list of inventors, along with the requisite Statement from Mr. Ruben, Assignment from Mr. Ruben to co-assignee Human

Genome Sciences, Inc., Consent of Co-Assignee Human Genome Sciences, Inc., Consent of Co-Assignee Delta Biotechnologies, new Declaration by the inventors of the application as originally filed, and Supplemental Application Data Sheet. Thus, the correct inventive entity of the present application *as originally filed* should be: Craig A. Rosen, William A. Haseltine, David J. Ballance, Andrew J. Turner, and Steven M. Ruben.

Secondly, in view of the amendment of the claims as described above, Applicants have filed a Request to Delete Inventors Under 37 C.F.R. § 1.48(b) to delete David J. Ballance and Andrew J. Turner from the list of inventors. Upon grant of this request, the correct inventive entity of the present application should be: Craig A. Rosen, William A. Haseltine, and Steven M. Ruben.

Both requests are accompanied by a petition fee pursuant to 37 C.F.R. § 1.17(i). Applicants accordingly request that the inventorship be changed to reflect the correct inventive entity for this application: Craig A. Rosen, William A. Haseltine, and Steven M. Ruben.

**Rejection under 35 USC § 112, ¶2**

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for recitation of the variables X and Y from Tables 1 and 3. Applicants traverse this rejection. However, as amended, the claims no longer recite the variables X and Y. Accordingly, Applicants request that this rejection be withdrawn.

The claims are further rejected as indefinite for reciting the phrase "inserted into an albumin" in combination with specific amino acids in claim 1(m). Applicants traverse

this rejection. However, since this language does not appear in new claims 22-45, Applicants request withdrawal of this rejection as well.

The claims are also rejected as indefinite for reciting the phrase "albumin activity." Applicants traverse this rejection, and in particular disagree with the Examiner's position that the property of enhancing the shelf-life or serum half-life of proteins is not considered an "albumin activity." In any event, as the phrase "albumin activity" does not appear in new claims 22-45, Applicants also request that this rejection be withdrawn.

**Rejections under 35 USC § 112, ¶1**

Claims 1-18 have been rejected as allegedly not enabled by the specification with respect to (1) albumin variants, and (2) fragments and variants of therapeutic proteins.

Applicants respectfully disagree and traverse the rejection. Applicants have added new claims 22-45, to more clearly point out what Applicants regard as their invention. In particular, new claim 22 is the only independent claim and specifically recites, rather than a fusion of albumin to any therapeutic protein, an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides. While the GLP-1 polypeptide encompasses GLP-1 variants and fragments, the claim specifically recites "wherein said GLP-1 fragments or GLP-1 variants have GLP-1 activity." As described in Table 1, page 49, GLP-1 activity may be assayed in vitro, for example, using a [3-H]-glucose uptake assay as described in J. Biol. Chem. 1999 Oct. 22 274 (43): 30864-30873. Additionally, while the claimed fusion proteins encompass fusions to albumin

variants, the claims specifically recite "wherein said albumin fragment or albumin variant increases the serum plasma half-life of the unfused GLP-1 polypeptide." For the reasons developed below, Applicants believe that the claims both as amended and as rejected, are fully enabled.

To satisfy the enablement requirement, the specification must enable a person of ordinary skill in the art to practice a single use of the claimed polypeptides without undue experimentation. *See, e.g.,* MPEP §2164.01(c). The Federal Circuit has held that making the claimed species and screening them for function is acceptable, as long as the experimentation is not undue. Thus, the test is whether it would require undue experimentation to practice the invention. *See generally, Atlas Powder v. E.I. Du Pont de Nemours & Co.* 750 F.2d 1569, 224 U.S.P.Q. (BNA) 409 (Fed. Cir. 1984). Moreover, it is not necessary to describe in detail in the specification what is well known in the art. *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

*1. Albumin Variants*

First with respect to the rejection based on the term "albumin variants," the specification discloses on page 174, paragraph 152 that:

> The albumin portion of the albumin fusion proteins of the invention may be a variant of normal HA. . . . The term "variants" includes insertions, deletions and substitutions, either conservative or non conservative, where such

> changes do not substantially alter one or more of the oncotic, useful ligand-binding an non-immunogenic properties of albumin, or the active site, or active domain which confers the therapeutic activities of the Therapeutic proteins.

Additionally, the specification teaches that naturally occurring polymorphic variants of human albumin and fragments of human albumin were known at the time the instant application was filed. (Page 174, paragraph 153, citing EP 322 094 (copy enclosed)). *See also* Weitkamp et al., Ann. Hum. Genet. 37:219-226 (1973) (copy enclosed). In fact, even as early as 1992, over 100 naturally occurring variants (amino acid substitutions and protein truncations) of albumin, termed alloalbumins, were known to exist. *See, e.g.,* Minchiotti et al., Biochimica et Biophysica Acta, 119:232-8 (1992); Galliano et al., FEBS Letters 208(2):364-368 (1986); Galliano et al., FEBS Letters 233(1):100-104 (1988); Galliano et al., Hershfield et al., PNAS 87:8721-8725 (1990); Galliano et al., J. Biol. Chem. 261:4283-4287 (1986); and Weitkamp et al., Ann. Hum. Genet. 36:381-392 (1973) (copies enclosed). Thus, numerous examples of functional albumin variants were known to the skilled artisan well before the filing of the instant application and were available for use in the claimed invention.

In addition to the known albumin variants, the primary and secondary structure of albumin was also well characterized in the art well before the filing of the present invention. *See, e.g.,* Peters, Clin. Chem. 23(1):5-12 (1977) (copy enclosed). For example, the sequence and the topography of the structure of albumin were well-known. *See id., e.g.,* page 6, column 1, under the heading "Sequence and Covalent Structure" and Figure 1; and page 7, column 1, lines 9-13. Moreover, domains of albumin which were necessary for function were also well-known. *See id., e.g.,* page 8 column 1, under the heading "Binding of ligands." In addition, numerous albumin

fragments that retain their native conformation and perform the binding functions of native albumin were also well-known. *See id., e.g.,* page 7; column 1, under the heading "Isolated Fragments of Albumin." Thus, it would have been merely routine to envision, make, and use albumin variants in the claimed invention.

Furthermore, it would have been routine to make albumin variants and screen the variants to identify those that increase the serum plasma half-life of albumin. For example, Hershfield and colleagues (PNAS 88:7185-7189 (1991); copy enclosed) used directed mutagenesis to create "mutant" variants of the *E. coli* protein PNP containing one to three amino acid mutations and compared the PNP enzymatic activity and plasma half-life between the variant and the wild-type protein. They also generated polyethylene glycol (PEG) modified versions of both the wild-type and variant PNP proteins and compared the PNP activity and plasma half-life between the modified and unmodified PNP proteins. *See, e.g.*, the Results section, under the headings "Preparation and PEG Modification of Wild-Type and Mutant *E. Coli* PNP" and "Comparison of Wild-Type and RK3 *E.* coli PNP and PEG-PNP." The authors were easily able to determine which mutants retained PNP activity, as well as which PEG-modified PNP proteins had extended plasma half-life. *See, e.g.,* Table 1 and Figure 3 of the Hershfield et al. reference. Therefore, well before the time of filing the instant application, the skilled artisan could have routinely generated albumin variants and compared the serum plasma half-life of the albumin variants with the known plasma half-life of native albumin using the procedures disclosed in the Hershfield *et al.* reference.

In summary, Applicants submit that the structure and function of albumin was well known in the art at the time of filing of the instant invention. In addition, numerous functional albumin variants, including albumin fragments and naturally-occurring albumin mutations that had little or no effect on albumin function were also known in the art. Therefore, the experimentation required to use known albumin variants in the claimed fusion proteins would have been minimal and routine. In addition, methods of making albumin variants and screening for those that increase the serum plasma half-life of native albumin were routine in the art at the time the instant application was filed. Therefore, the disclosure of the instant application, in view of the extensive knowledge in the art of molecular biology, particularly with respect to albumin and its variants, provides adequate enablement for the claimed fusion proteins. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection based on the recitation of albumin variants under 35 U.S.C. § 112, first paragraph.

2. *Fragments and Variants of Therapeutic Proteins*

Secondly, with respect to the rejection based on the fragments and variants of the therapeutic proteins, Applicants again point out that the instant claims are directed to albumin fusion proteins comprising "two or more tandemly oriented GLP-1 polypeptides, wherein said GLP-1 polypeptides are selected from wild-type GLP-1, GLP-1 fragments, or GLP-1 variants, wherein said GLP-1 fragments or GLP-1 variants has GLP-1 activity." The terms "fragments" and "variants" as they apply to the therapeutic protein GLP-1 recited in the claims are fully described in the specification as filed, for example, on pages 154-167, paragraphs 88-127. The specification also

discloses numerous GLP-1 fragments and variants, for example, in Table 2 and in the Sequence Listing. For example, GLP-1(7-36) is disclosed às SEQ ID NO:630; GLP-1(7-36(A8G)) is disclosed as SEQ ID NO:633; and GLP-1(9-36) is disclosed as amino acids E100 to R127 of preproglucagon (SEQ ID NO:1249). Additionally, the specification describes how to test for GLP-1 activity of the GLP-1 fragments and variants. For example, the specification states in Table 1 on page 49 that "GLP-1 activity may be assayed in vitro using a [3-H]-glucose uptake assay," as described in Urso et al., J. Biol. Chem., 274: 30864-30873 (1999) (copy enclosed). Thus, the specification more than adequately enables the claims as amended.

Furthermore, at the time of filing of the present invention, the skilled artisan was well aware that GLP-1 "is a 30-residue gastrointestinal hormone released from the enteroglucagon cells (L-cells) in the small intestine" that "plays an important role in the postprandial regulation of insulin secretion." Gallwitz et al., Eur. J. Biochem. 225: 1151-1156, 1151, par. 1 (1994) (copy enclosed). GLP-1 was also readily available from chemical supply companies at least as early as 1994. *See id.* at 1151, last sentence in col. 2. Additionally, the amino acid sequences of human and pig GLP-1 have been known since at least 1989. *See, e.g.,* Orskov et al., J. Biol. Chem., 264: 12826-12829 (1989) (copy enclosed).

Based on the sequence, structural, and functional information known in the art at the time of the instant application's filing, one skilled in the art was capable of making fragments and variants of GLP-1 with a reasonable expectation of success, as demonstrated by the extant scientific literature at the time the present application was filed. For example, as early as 1989, Suzuki et al., Endocrinology, 125: 3109-3114

(1989) (copy enclosed) described GLP-1 fragments and their stimulatory effects on insulin release. And in 1991, Schmidtler et al., Am. J. Physiol. 260:G940-950 (1991) (copy enclosed) stated that "[t]he insulinotropic effect of [the fragment] GLP-1-(7-36) amide has been extensively studied." *See* page G940, col. 2, first full paragraph. The article also describes additional GLP-1 variants. *See id.* at G941-942. Additionally, Adelhorst et al., J. Biol. Chem., 269: 6275-6278 (1994) (copy enclosed) described a series of GLP-1 variants, as well as an in vitro GLP-1 receptor binding assay to measure the structure-activity relationship of GLP-1. *See also,* Hjorth et al., J. Biol. Chem., 269: 30121-30124 (1994) (copy enclosed); Gallwitz et al., Eur. J. Biochem. 225: 1151-1156 (1994) (copy enclosed); Parker et al., J. Peptide Res., 52: 398-409 (1998) (copy enclosed). Similarly, U.S. Pat. No. 5,545,618 to Buckley et al. (issued in 1996) (copy enclosed) described analogs of GLP-1 that enhance the peptide's utility in treatment of diabetes. *See* col. 1, line 44-col. 2, line 13, describing early fragments and variants of GLP-1 as well as the '618 patent's invention relating to analogs of GLP-1 fragments.

Taken together, the above evidence clearly shows that sufficient structural-functional information about GLP-1 existed well before the filing date of the instant application to enable one skilled in the art to make fragments or variants of GLP-1 with a reasonable expectation of success. Thus, the invention as claimed is enabled and Applicants respectfully request that the rejection be withdrawn.

**Rejections under 35 USC § 102**

*1. Rejection over Delta Biotechnology (WO 97/24445)*

Claims 1-4, 6, and 11-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Delta Biotechnology (WO 97/24445) ("Delta '445"). The Office alleges that Delta '445 teaches fusion proteins of human growth hormone and albumin, expressed preferentially in yeast, which exhibit enhanced storage stability and serum half-life. However, the claims now recite "two or more tandemly oriented GLP-1 polypeptides." Delta '445 does not teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides. Thus, Delta '445 does not anticipate the claims, and withdrawal of the rejection is respectfully requested.

*2. Rejection over Fleer et al. (US 5,876,969)*

Claims 1-6 and 9-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fleer et al. (US 5,876,969) ("Fleer '969"). The Office alleges that Fleer '969 teaches fusion proteins of therapeutic proteins and albumin, exhibiting enhanced shelf life and serum half-life. However, the claims now recite "two or more tandemly oriented GLP-1 polypeptides." Fleer '969 does not teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides. Thus, Fleer '969 does not anticipate the claims, and withdrawal of the rejection is respectfully requested.

*3. Rejection over Human Genome Sciences (WO 02/097038 A3)*

Claims 1-4 and 14-16 are rejected under 35 U.S.C. § 102(e) as being anticipated by Human Genome Sciences (WO 02/097038 A3) ("HGS '038"). The Office alleges that

HGS '038 teaches fusion proteins with ckbeta1 and albumin. However, the claims now recite "two or more tandemly oriented GLP-1 polypeptides." HGS '038 does not teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides. Thus, HGS '038 does not anticipate the claims, and withdrawal of the rejection is respectfully requested.

*4. Rejection over Human Genome Sciences (WO 03/030821 A2)*

Claims 1-18 are rejected under 35 U.S.C. § 102(e) as being anticipated by Human Genome Sciences (WO 03/030821 A2) ("HGS '821"). The Office alleges that HGS '821 teaches fusion proteins with human growth hormone and albumin. However, the claims now recite "two or more tandemly oriented GLP-1 polypeptides." HGS '821 does not teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides. Thus, HGS '821 does not anticipate the claims, and withdrawal of the rejection is respectfully requested.

*5. Rejection over Human Genome Sciences (US 2003/0171267 A1)*

Claims 1-18 are rejected under 35 U.S.C. § 102(e) as being anticipated by Human Genome Sciences (WO 2003/0171267 A1) ("HGS '267"). The Office alleges that HGS '267 teaches fusion proteins with albumin and calcitonin, growth hormone releasing factor, interferon β, and parathyroid. However, the claims now recite "two or more tandemly oriented GLP-1 polypeptides." HGS '267 does not teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides.

Thus, HGS '267 does not anticipate the claims, and withdrawal of the rejection is respectfully requested.

**Double Patenting Rejections**

*1. Provisional Rejection under 35 U.S.C. § 101 over Appln. No. 09/833,117*

Claims 1-18 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-26 and 60-71 of copending Application No. 09/833,117. Applicants submit that the instant claims, which are directed to albumin fusion proteins comprising two or more tandemly oriented GLP-1 polypeptides, are not the same as the claims of copending Application No. 09/833,117. Thus, Applicants request that the provisional rejection be withdrawn.

*2. Provisional Rejection under 35 U.S.C. § 101 over Appln. No. 10/816,042*

Claims 1-18 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-26 of copending Application No. 10/816,042. Applicants submit that the instant claims, which are directed to albumin fusion proteins comprising two or more tandemly oriented GLP-1 polypeptides, are not the same as the claims of copending Application No. 10/816,042. Thus, Applicants request that the provisional rejection be withdrawn.

*3. Provisional Rejection under 35 U.S.C. § 101 over Appln. No. 10/153,604*

Claim 1 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 4-7 and 14-16 of copending Application No. 10/153,604.

Applicants submit that the instant claims, which are directed to albumin fusion proteins comprising two or more tandemly oriented GLP-1 polypeptides, are not the same as the claims of copending Application No. 10/153,604. Thus, Applicants request that the provisional rejection be withdrawn.

*4. Provisional Rejection under 35 U.S.C. § 101 over Appln. No. 10/775,180*

Claims 1-18 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-29 of copending Application No. 10/775,180. Applicants submit that the instant claims, which are directed to albumin fusion proteins comprising two or more tandemly oriented GLP-1 polypeptides, are not the same as the claims of copending Application No. 10/775,180. Thus, Applicants request that the provisional rejection be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: April 26, 2005

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